Original Article

RESULTS OF CHEMOTHERAPY BY UKCCSG PROTOCOL IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA: CLINICAL CHARACTERISTICS AND OUTCOME

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ABSTRACT

Objectives: Acute lymphoblastic leukemia (ALL) represents a clonal expansion and arrest of normal lymphoid hematopoiesis. ALL remains the most common malignancy in children. The survival rate of the patients is significantly increased since the 1960s. This study was undertaken to evaluate the 5- year overall survival (OS) rates of patients with ALL in a single center in IRAN.

Methodology: A total of 220 children with ALL up to 15 years old who had been treated by UKCCSG protocol at the Oncology Department in Shafa Hospital from March 1997 to October 2004 were evaluated for their age, gender, as well as FAB types, presenting features, outcomes of therapy and relapse.

Results: The mean age of the patients was 6.69 years (SD= 3.8, median 6 years). In this series, 123 patients (55.9%) were male. There was a complete remission induction rate of 85.5% during first induction course of therapy. Five-year overall survival was 60.9% and it was better (p=0.006) in standard risk group. Relapse rate after first remission was 23.6% and death due to relapse was more in high risk group, but it was not significant (p=0.053). There were 59(68.6%) of total deaths in induction period and 18(20.9%) after relapse. Overall infections (69.4%) were major cause of deaths in induction period. OS was better in boys, age group between (1-10 yo) and initial white blood cells count (10,000-50,000x10^3/mm^3) but there were not significant (p=0.39, p=0.30, p=0.202, respectively).

Conclusion: Five-year overall survival was 60.9% of the children with new ALL who were undergoing chemotherapy by UKCCSG protocol. High mortality rate in induction period was mainly due to infections which decreased five-year overall survival in this study.

KEY WORDS: Acute lymphoblastic leukemia, UKCCSG, Survival.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) represents a clonal expansion and arrest at a specific stage of normal lymphoid hematopoiesis.[1] ALL remains the most common malignancy in children. It accounts for one fourth of all childhood cancers and approximately 75% of all cases of childhood leukemia.[2] The peak incidence of

ALL occurs between two to five years of age.[3] Although more than 5% lymphoblast, in the bone marrow is highly suggestive of leukemia, a minimum of 25% blast cells is usually required before the diagnosis is confirmed.[4] Central nervous system leukemia (CNS) is found at diagnosis of fewer than 5% of children with ALL.[5] Clinically demonstrable testicular disease is rarely present at initial diagnosis but occult testicular disease can be diagnosed by biopsy in 25% of newly diagnosed boys.[6]

The French-American-British (FAB) system defines three categories of lymphoblasts. Approximately 85% of children with ALL have predominant L1 morphology, 14% have L2 and 1% have L3.[7] Patients who are between ages one and nine with an initial White Blood Cells (WBCs) < 5,0000 /mm^3 were defined as standard risk.[1] In 1977 the Unite Kingdom Children's Cancer Study Group (UKCCSG) was formed by a small number of consultants from seven hospitals. The group has since expanded until it now covers 20 pediatric oncology centers in mainland Britain together with two in Ireland.[8]

The purpose of this study was to evaluate the five- year overall survival (OS) rates of patients with ALL who were treated by UKCCSG protocol at our department and also the related factors.

METHODOLOGY

From March 1997 to October 2004, 220 patients (age under 15 years) with ALL were diagnosed and treated in Hematology/Oncology Department at Shafa Hospital. The children were subdivided into three age groups: infancy < one year olds, one to nine year olds, and 10 to 15 year olds. Their gender, sex, FAB type, clinical features, first remission rate, relapse rate, death in induction, death in relapse, Overall survival (OS), Disease-Free survival (DFS), and Events-Free survival (EFS) were compared between age group by MINITAB 14 software.

Median follow up was seven years (range, 5 days to 12 years 6 months). Complete remission (CR) was defined as a normocellular bone marrow examination containing less than 5% blast cells. Deaths within 30 days of entry were classified as induction deaths. OS was defined as an indication of the proportion of people within a group who are expected to be alive after a specified time. Disease-free survival (DFS) was defined as measures the proportion of people among those treated for cancer who will remain free of disease at specified time after treatment. Event-free survival (EFS) was defined as a measure of the proportion of people who remain free of a particular complication of disease (called an event) after treatment that is designed to prevent or delay that particular complication.

In this study the patients were classified into two risk groups, standard and high risk groups. Standard risk patients included age between one to nine with an initial WBC < 50,000/mm.^{3} High risk patients included age under one year and over than 10 year or with initial WBC > 50,000/mm.^{3} A p value < 0.05 was considered statistically significant. Relapse was evaluated in three separate period of time, during 6 months, 6-18 months and 18 months after first remission. The patients were treated according to the UKCCSG protocol. The patients were stratified within the treatment groups according to prognostic criteria. Girls between one to nine year of age with a WBC count less than 20,000/mm^3 were scheduled to receive treatment A. Patients with a WBC count greater than 100,000/mm^3 were scheduled to receive treatment D. Another girls and boys were scheduled to received treatments B and C respectively. Summary of treatment, Upon completion of induction, patients were divided into four treatment groups as above. All patients received the same induction chemotherapy, utilized Vincristine, Prednisolone, L-asparaginase, Daunorobicine and intrathecal Methotrexate. The drugs utilized in intensification were Vincrisine, Prednisolone, Daunorobicine, Thioquanine, VP16, Ara-C and intrathecal Methotraxate. Patients were randomized to receive either one block of intensification, given immediately after induction (treatment B), one block of intensification administered after cranial irradiation (18 Gy) at weeks 20 of maintenance (treatment C), or to receive both early and

late intensification blocks (treatment D) and in treatment A the patients did not receive any intensification block. A 12 weeks cycle of continuance daily Mercaptopurine and weekly Methotrexate, with a monthly injection of Vincristine followed by a short pulse of Prednisolone, to a total of 40 to 48 month according to treatment group and also intrathecal Methotrexate on the first day of each cycle were considered as maintenance therapy. To confirm continued remission bone marrow aspiration and lumbar punctures at the beginning of each cycle were obligatory.

RESULTS

In the 220 patients with ALL up to 15 years old their mean age at diagnosis was 6.69 (sd = 3.8). One hundred twenty three patients (55.9%) were male and 97(44.1%) female. Four patients (1.8%) were below one year, 162(73.6%) 1-9 years, 54(24.5%) 10-15 years. Comparison of presenting features showed that fever (64.4%), pallor (53.6%), splenomegaly (48.6%), hepatomegaly (46.3%), lymphadenopaty (45%), and bone pain (34%) were more frequent in children. FAB types L1 (77.7%) and L2 (18.6) were more frequent in the children (Table-I). Treatment A was used in 38(17.3%) of the patients, B 12(5.5%), C 84(38%) and D 85(36.7%) (Table-III). The duration from initial diagnosis to the end of study was 12.5 years. The minimum five-year OS, DFS and EFS for 220 patients was 60.9%, 49.1% and 11.8% respectively. For males the five-year OS were 63.4% and for females 57.7% (*p* 0.303). The five-year OS in patients below one year were 0%, one to nine years 66% and 10 to 15 years 50%. There was no significant difference in OS with age (p=0.302), initial WBCs count (p=0.209), FAB types (p=0.535) and treatment groups (p=0.115). But there was significant trend in OS with risk groups (p=0.006).

There was no significant difference in age at diagnosis of ALL with gender (p=0.548), initial WBCs count (p=0.522), FAB types (p=0.254), CNS involvement (0.144) and first remission rate (0.765). Relapse risk after first remission for

Table-I: Characteristics of 220 patients up to 15 years diagnosed with ALL, 1997-2004

		Age (yo)		
Parameter	*No. of patients & % n=220 (100)*	*<1 n=4*	*1-9 n=162*	*10-15 n=54*
Gender:				
Male	123(55.9)	1	91	31
Female	97(44.1)	3	71	23
Clinical finding:				
Fever	144(65.4)	3	110	31
Pallor	118(53.6)	0	91	27
Bone pain	75(34)	1	57	17
Lymphadenopaty	99(45)	2	66	28
Hepatomegaly	102(46.3)	3	78	21
Splenomegaly	107(48.6)	3	78	26
Petechiae	33(15)	0	26	7
GI bleeding	5(2.2)	0	4	1
Epistaxi	9(4)	0	6	3
Testis involvement	1(0.5)	0	0	1
CNS involvement	12(5.4)	0	7	5
Sweating	21(9.5)	0	15	6
Weight lose	18(8.1)	0	13	5
Anorexia	26(11.8)	1	17	8
Diarrhea	6(2.7)	0	4	2
Abdominal pain	8(3.6)	0	7	1
FAB Types				
L1	175(77.7)	2	134	39
L2	37(19.6)	2	23	12
L3	8(3.6)	0	5	3
Risk groups				
Standard risk	119(54.1)	0	119	0
High risk	101(46.9)	4	43	24

Table-II: Outcomes of patients with ALL

		Age (yo)		
Parameter	*No. of patients & % n=220 (100)*	*<1 n=4*	*1-9 n=162*	*10-15 n=54*
Survival				
Overall- survival	134(60.9)	0	107	27
Disease-free survival	108(49.1)	0	88	20
Event-free survival	26(11.8)	0	19	7
First remission				
Complete remission	188(85.5)	3	140	45
No remission	32(14.5)	1	22	9
Deaths				
In induction	59(26.8)	2	41	16
After relapse	18(8.1)	0	10	118
After induction Without relapse	9(4.1)	2	4	3
Relapse after induction	*No. of patients & % n=161*			
Relapse	38(17.3)			
Bone marrow	26(17.3)	--	17	9
CNS	16(9.9)	--	9	7
Testis	3(1.8)	--	3	0

the children who were undergoing chemotherapy by UKCCSG protocol was 38(23.6%) in our study. Relapse from Bone marrow occurred in 26(17.3%) of patient, CNS 16(9.9%) and testis 3(1.8%) (Table-II). There was no significant correlation in age groups (p=0.146), initial WBCs count (p=0.148), FAB types (p=0.506) and risk groups (p=0.357) with relapse. But there was significant trend in deaths after relapse with increasing age at diagnosis of ALL (p=0.026). There was significant correlation in CNS relapse with age groups (p=0.043) and lymphadenopathy (p=0.010). There were 86(39.09%) of deaths. Fifty nine (26.8%) deaths occurred in induction period, 18(8.2) after relapse and 9(4.1%) after induction period without any evidence of relapse (Table-II). The major causes of deaths in induction period were sepsis 29(49.1%), typhilytis 12(20.3%), cardiac 6(10.1%), renal 5(8.4%) and CNS 3(5%) complications. The prognosis after relapse was better after 6 months of remission and also in testis relapse, but it was not significant (p=0.712, p=0.792 respectively). Deaths after relapse was more in high risk group but it was not significant (p=053). There was significant correlation in first remission rate with FAB type (p=0.006). There was significant trend in bone pain with standard risk group (p=0.021) and low initial WBCs count (p=0.007). Blasts were detected on initial peripheral smear of 84(38.2%) patients with significant trend in high initial WBCs count (p=0.001). Also there was significant correlation in splenomegaly with hepatomegaly (p=0.033), lymphadenopathy (p=0.005) and risk groups (p 0.0.046).

DISCUSSION

Five year survival rate for children diagnosed in successive calendar periods were 69% in 1980-84, 74% in 1985-89 and 81% in 1990-94. The improvement in survival was highly significant overall (p=0.0001).[8] Survival outcomes for patients treated on successive children's cancer group (CCG) clinical trials conducted over the 1968-2004 period, approximately was 18% in 1968-70 and 85% in 1996-2002.[9] Survival did not vary significantly between hospitals with different numbers of patients or between UKCCSG and other hospitals during a big study of 5078 children with ALL in 1980-94 by C A Stiler et al. For example UKCCSG 5- year survival was 82% and 79% others center during 1990-94.[8] In the 220 patients with ALL up to 15 years old who were treated by UKCCSG protocol five-year OS was 60.9% in our study at SHAFA Hospital from Jondishapoor Ahwaz medical university in IRAN as a developing country. Complete remission induction rate of children with ALL according to the chemotherapy regimens is approximately 85% to 95%.[10]

Failure of induction therapy is a relatively rare event, occurring in fewer than 5% of children with ALL treated with correct regimens.[11] Like

Table-III: The five-year survival rates of patients with ALL

Factors	*No. of Patients*	*%*	*5 year survival rate (%)*	*p value*
Overall	134	60.9	60.9	---
Gender				0.393
Male	123	55.9	63.4	
Female	97	44.1	57.7	
Age (yo)				0.302
<1	4	1.8	0	
1-9	162	736	66	
10-15	54	24.5	50	
Initial WBCs/mm3				0.209
<10.000	95	43.2	63	
10.000-50.000	67	30.5	65	
>50.000	58	26.4	51	
Initial Hb g/dl				
<7	90	40.9		
7-10	107	48.6		
>10	23	10.4		
FAB types				0.535
L1	175	77.7	62.2	
L2	37	18.6	54	
L3	8	3.6	62.5	
Treatment group				0.115
A	38	17.3	78.9	
B	12	5.5	33.3	
C	85	38.6	58.8	
D	85	38.6	58.8	
Risk groups				0.006
Standard risk	119	54.1		
High risk	101	45.9		
Relapse	38	23.6		
Relapse time of diagnosis (Months)				
<6	8	21		
6-18	13	34.2		
>18	17	44		

these, reports there was a complete remission rate of 85.5% during first induction course of therapy in our study. Despite acceptable first remission rate, the high mortality rate in induction period (68.6% of total deaths), reduced outcome in our center. Investigators at St Jude Children's Research Hospital have demonstrated that after successful completion of 2.5 years of therapy, approximately 80% of patients remain free of disease.[9] Similar results were observed in a study from Great Britain that concluded that patients alive 6 years after diagnosis without relapse have a high likelihood of prolonged survival and cure.[12]

Like other studies, relapse rate after first remission was 38(23.6%) in our study. Despite current intensive treatments, 25-30% of children with ALL experience bone marrow relapse.[1] Bone marrow relapse rate in our study was only 26(17.3%), it shows that long- term duration of maintenance therapy (40-48 months versus 24-36 months) reduce the relapse rate.[13,14] Long-term survival rate in relapse after 6 months of remission was better in our study, but it was not significant (p=0.712). As reported by other investigators we found that children aged 1-9 at diagnosis and those with WBCs of under 50,000/mm^3 had a better prognosis and the combination of these two factors has been proposed as defining a good risk subgroup (p=0.006).[15] A slightly lower survival rate in girls was in contrast to previous studies.[16] Maybe it is due to more attention for male gender by parents in our region. There was significant trend in bone pain with low risk group (p=0.021) and low initial WBCs count (p=0.007) as a report by Jonsson et al[17], that initial WBCs count were usually normal in ALL patients who had severe bone pain. Clinical and laboratory features at diagnosis in children with acute lymphocytic leukemia in our study almost were like other studies.[9]

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